IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	) Examiner: Hamud, Fozia
Avi ASHKENAZI, *et al.*	) Art Unit: 1647
Application Serial No. 09/997,573	) Confirmation No: 3279
Filed: November 15, 2001	) Attorney's Docket No. 39780-2730 P1C45
For: **PRO1375 POLYPEPTIDES**	) **Customer No. 35489**

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ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES APPELLANTS' REPLY BRIEF

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents -
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

On November 24, 2004, the Examiner made a final rejection to pending Claims 119-127 and 129-131. A Notice of Appeal was filed on February 24, 2005 and an Appellants' Appeal Brief was filed September 23, 2005. An Examiner's Answer was mailed on April 24, 2006. A Reply Brief was mailed on June 23, 2006. An amended Examiner's Answer was mailed on November 3, 2006.

The following constitutes an Appellants' Reply Brief in response to the second Examiner's Answer and is timely filed. This Reply Brief is accompanied by a Request for Oral Hearing.

ARGUMENTS

I. Priority

For the reasons outlined in their Appeal brief of January 13, 2006 and discussed below, Appellants maintain that the instant application is entitled to the earlier priority date of U. S. Application Serial No. 60/144,758 filed **July 20, 1999**, for the claimed PRO1375 polypeptides.

II. *Claim Rejections Under 35 U.S.C. §101 and §112, First Paragraph*

Appellants submitted that patentable utility for the instantly claimed PRO1375 polypeptide is based upon the data derived from the mixed leukocyte reaction (MLR) assay, as disclosed in Example 151 of the instant specification. Example 151 shows that PRO1375 tested positive in the mixed lymphocyte reaction (MLR) assay and therefore, is an immunoenhancer, which has utility in the treatment of conditions where the enhancement of an immune response would be beneficial (like increasing immunosurveillance in cancer). The Examiner has acknowledged the value of the MLR assay, which is a well known assay in the art, based upon the teachings within U.S. Patent No. 5,817,306 and says that: "the MLR assay and phytohemagglutinin A (PHA) assays are valuable for identifying immune suppressive molecules in vitro that are useful for treating graft versus host disease. The results obtained from these assays are generally predictive of their in vivo effectiveness (see column 12, lines 36-41 of U.S. Patent No. 5,817,306)." However, the Examiner maintains the rejections to Claims 119-127 and 129-131 under 35 U.S.C. §101 as allegedly lacking a specific, substantial and credible asserted utility or a well established utility. The Examiner cites the following arguments:

(1) Regarding the instant disclosure, the Examiner asserts that "(t)he specification **does not provide any values or data** for the proteins tested in the assay....**(no) statistics** for the values measured....no information regarding the results of the assay except that a certain protein tested positive" (emphasis added; page 7, lines 3-6 of the Examiner's Answer). The Examiner adds that "(t)here is insufficient data presented, as well as insufficient controls used, to conclude anything regarding the ability of the claimed polypeptide to be used in a substantial way to therapeutically (enhance) the immune response of an individual, and "further experimentation

would be required to use the invention in this manner" (page 8, lines 18-22 of the Examiner's Answer). Regarding the Fong Declaration, "The Fong declaration evinces that the instant specification provides a mere invitation to experiment, and not a readily available utility. The PRO1375 protein has not been shown to therapeutically enhance the immune system. The specification merely demonstrates that the PRO1375 protein increases T-cell proliferation above control." (page 14, lines 6-10 of the Examiner's Answer).

Appellants disagree with each of the Examiner's arguments for the reasons detailed below. The Examiner's arguments will be addressed in the order in which they are listed above.

Arguments:

Appellants assertion for utility for the PRO1375 polypeptide is based on a positive result in the MLR assay, which the Examiner has acknowledged as being a well known assay in the art, and which is valuable for identifying immunostimulants (also referred to as immune enhancers) *in vitro*. Such molecules are useful, in the treatment of viral infections or cancer, for example, or for treating diseases like graft versus host disease. Based on their identification of PRO1375 as an immunosuppressive molecule, one skilled in the art would find it credible that PRO1375 is useful in the treatment of conditions where the enhancement of an immune response would be beneficial. The specification expressly states that, in the MLR assay, positive increases over control, especially increases of greater than or equal to 180% is preferred. Yet the Examiner asserts that "further experimentation would be required to use the invention in this manner."

Appellants respectfully disagree. Regarding the need for "values or data for the proteins tested in the assay" or "statistics for the values measured," the remarks are a clear indication that the Examiner applies a standard that might be appropriate if the issue at hand were the regulatory approval of a drug based on the immunoenhancer activity of PRO1375, but is fully inappropriate for determining if the "utility" standard of the Patent Statute is met. The FDA, reviewing an application for a new immunoenhancer drug, will indeed ask for actual numerical data, statistical analysis, and other specific information before the drug is approved. However, the Patent and Trademark Office is not the FDA, and the standards of patentability are not the same as the standards of market approval. It is well established law that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and

efficacy of drugs to marketed in the United States.[1] Indeed, in *Nelson v. Bowler,*[2] the Federal Circuit found that the identification of a pharmacological activity of a compound provides an "immediate benefit to the public" and satisfies the utility requirement. This logically applies to the instant utility as well. The identification of a compound as an immunoenhacer should suffice to establish an "immediate benefit to the public" and thus to establish patentable utility.

The MLR assay described herein is a comparative one, meaning that the utility is based upon a comparison of relative expression levels between a known polypeptide and an unknown PRO molecule. Useful information is obtained when a relative differences are observed, and this is routine in biological testing. All that is important for utility is that the difference is significant and Appellants expressly assert that the observed difference for PRO1375 is significant. For instance, the specification expressly states that, in the instant MLR assay, positive increases over control, especially increases of greater than or equal to 180% is preferred and that PRO1375 tested positive in this assay. The Examiner seems to focus on exactly how much higher (*i.e.,* requiring Applicants to provide "relative or absolute levels" and statistical analyses), but Applicants submit that this is not relevant to the issue at hand, nor is it required for the claimed invention to be useful.

Appellants further respectfully remind the Examiner that an Applicants' assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "**unless there is a reason for one skilled in threat to question the objective truth of the statement of utility or its scope.**" (emphasis added) *In re Langer*, 503 F.2d 1380, 1391, 183 U.S.P.Q. (BNA) 288, 297 (C.C.P.A. 1974). *See also In re Jolles*, 628 F.2d 1322, 206 U.S.P.Q. 885 (C.C.P.A. 1980); *In re Irons*, 340 F.2d 974, 144 U.S.P.Q. 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 U.S.P.Q. 209, 212-13 (C.C.P.A. 1977). Compliance with 35 U.S.C. §101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. (BNA) 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence,

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[1] *Scott v. Finney*, 34 F.3d 1058, 1063, 32 U.S.P.Q.2d 1115, 1120 (Fed. Cir. 1994).

[2] *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. *M.P.E.P.* at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The Examiner has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." (emphasis added) *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Appellant to provide rebuttal evidence. *Id.* The Examiner has not cited a single reference that would show that one of ordinary skill in the art would reasonably doubt the asserted utility. Accordingly, a proper prima facie case has not been made in this instance and the burden to rebut this rejection has not entirely shifted to the Appellants.

Yet, Appellants provided the Fong Declaration to explain how the MLR reaction was performed in the instant application using peripheral blood mononuclear cells (PBMCs). In fact, the Fong Declaration detailed the state of the art, at the time of filing, in the field of immunostimulation/ suppression and provided art accepted examples of the usefulness for such immunostimulant molecules. Based on these teachings, it is more likely than not that one skilled in the art, to a reasonable probability, would believe that the claimed polypeptide is useful as an immunostimulant. Further, the present application discloses this utility for PRO1375 such that one of skill in the art would know exactly how to use the claimed polypeptides as immunostimulants, for instance, for immunesurveillance in diseases like cancer, without any undue experimentation. The specification also provides detailed guidance on how to identify and make polypeptides having amino acid sequence identity to PRO1375 polypeptides. Thus, Appellants believe that this rejection of Claims 119-127 and 129-131 should be withdrawn.

III. ***Claim Rejections Under 35 U.S.C. §112, First Paragraph- Written Description***

Applicants maintain that the specification provides ample guidance to allow the skilled artisan to identify those polypeptide variants which meet the recitations of Claims 119-123, including a detailed protocol for the MLR assay. The specification also provides detailed guidance as to how to identify and make polypeptides having at least 80% amino acid sequence identity to PRO1375 (SEQ ID NO:418). Accordingly, one of ordinary skill in the art would know that Appellants had possession of the recited polypeptide variants.

IV. ***Claim Rejections Under 35 U.S.C. §102***

Appellants maintain that, based on an effective filing date of **July 20, 1999** for the instant application, which is over six months before the publication date of WO00/18904, WO00/00610, WO00/00506, and at least one month before the publication date of WO99/63088, neither of the cited references are prior art. Similarly, the effective filing date of **July 20, 1999** for the instant application is over six months before the publication date of EP1130094, which therefore, is also not prior art. Appellants maintain that this rejection should be withdrawn.

CONCLUSION

For the reasons given above, Appellants submit that the MLR assay disclosed in Example 151 of the specification provides at least one patentable utility for the PRO1375 polypeptides of Claims 119-127 and 129-131, and that one of ordinary skill in the art would understand how to used the claimed polypeptides, for example in therapeutic applications where enhancement of an immune response is beneficial, such as the treatment of viral infections or cancer. Therefore, Claims 119-127 and 129-131 meet the requirements of 35 USC §101 and 35 USC §112, first paragraph. Further, this patentable utility for the claimed polypeptides was first disclosed in U.S. Provisional Application Serial No. 60/144,758, filed on July 20, 1999, priority to which is properly claimed in the instant application. Accordingly, the instant application has an effective priority date of July 20, 1999, and therefore neither WO00/18904, (published June/2000); WO99/63088, (published September/1999); WO00/00610, (published June/2000); WO00/00506, (published June/2000) nor EP1130094, (published September/2001) are prior art

and they do not anticipate the claims under 35 USC §102(a) or (b).

Accordingly, reversal of all the rejections of Claims 119-127 and 129-131 is respectfully requested.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2730 P1C45**).

Respectfully submitted,

Date: January 3, 2007

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